

Prevalence and comorbidities of bronchiolitis in adults

A population-based study in South Korea

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Abstract

Bronchiolitis generally refers to inflammation and/or fibrosis of the non-cartilaginous small airways located approximately from the 8th airway generation down to the terminal and respiratory bronchioles. In contrast to young children, the frequency of small airway infection in adult bronchiolitis appears less frequent and a number of other pathophysiological conditions have been implicated in adult bronchiolitis. However, little information is available on the exact medical burden of bronchiolitis such as its prevalence and comorbidities in the adult population. The aim of this study is to elucidate the prevalence and comorbidities of bronchiolitis. We used the Korea National Health Insurance Service-National Sample Cohort, which provides data for 1,000,000 individuals out of the entire population by 2% stratified random sampling according to age, sex, residential area, and level of household income. We defined the cause of bronchiolitis other than acute infection as a patient with diagnostic code J448 or J684 and over 20 years of age who visited a clinic or hospital in South Korea. Then, 1:1 propensity score matching was performed to define a non-bronchiolitis (control) group to compare the comorbidities and mortality in the 2 groups. The overall prevalence of bronchiolitis was 688 cases/1,000,000 population during the study period (95% confidence interval, 625–751). The most common comorbid clinical condition in adults with bronchiolitis was rhinitis (52.3%), followed by bronchial asthma (52.23%), hypertension (43.69%), gastroesophageal reflux disease (30.56%), sinusitis (28.72%), diabetes (22.77%), and osteoporosis (17.85%). Other common bronchiolitis-associated comorbidities were cerebrovascular disease (16.86%), angina (14.37%), peripheral vascular disease (13.42%), congestive heart failure (11.9%), and malignancy in any organ (10.6%). Healthcare costs for bronchiolitis increased steeply during the same period. Malignancy in any organ was the leading cause of mortality in the patient group, followed by bronchiolitis itself. Further larger prospective multiethnic cohort studies should be carried out in the near future.

Abbreviations: CHF = congestive heart failure, CVD = cerebrovascular disease, GERD = gastroesophageal reflux disease, HTN = hypertension, ICD-10 = International Classification of Diseases, 10th revision, KNHIS-NSC = Korea National Health Insurance Service-National Sample Cohort.

Keywords: bronchiolitis, epidemiology, National Health Insurance Service, respiratory tract diseases

JSJ and JSK contributed equally to this study.

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Bronchiolitis generally refers to inflammation and/or fibrosis of the non-cartilaginous small airways located approximately from the 8th airway generation down to the terminal and respiratory bronchioles. This portion of the airways is particularly vulnerable to obstruction.^[1,2] Given the abundance and centrilobular distribution of bronchioles between the major airways and lung parenchyma, bronchiolitis may represent one of the major pathologic conditions leading to a significant limitation of airflow^[3]; however, its clinical importance has been underestimated.^[4,5]

In contrast to young children, the frequency of small airway infection in adult bronchiolitis appears less frequent and a number of other pathophysiological conditions have been implicated.^[1] However, little information is available on the exact medical burden of bronchiolitis such as its prevalence and comorbidities in the adult population. Therefore, in this study, we investigated several cardinal clinical aspects of adult bronchiolitis in the Asian population, including its prevalence, associated comorbidities, and mortality.

2. Methods

2.1. Ethical considerations

All studies were performed following the requirements of the Declaration of Helsinki and using Korea National Health Insurance Service-National Sample Cohort (KNHIS-NSC). This study was approved by the Institutional Review Board of the Biomedical Research Institute of Jeonbuk National University Hospital (IRB number 2019-11-046). KNHIS-NSC data are anonymized for research purposes, thus written informed consent was not required.

2.2. Database

KNHIS-NSC is a 2% randomly stratified sampled cohort representing the total population of 50 million in South Korea (NHIS-2021-2-235). This database includes information such as the identification information for the individual, age, sex, residential area, and household income, diagnostic code, medical expenditure, treatment history, and prescription details including medication. The selected sample cohort divided approximately 1,025,340 individuals into 18 categories of age, 2 categories of sex, 41 categories of income level, and 17 categories of residential area, which is representative of the 50 million people in South Korea.

2.3. Study population

In this study, we defined adult patients having bronchiolitis from causes other than acute airway infection as follows: patients who visited hospital in the period January 1, 2002 to December 31, 2013; patients who had International Classification of Diseases, 10th revision (ICD-10) diagnosis codes J448 or J684; patients aged 20 years or older; and patients who were confirmed to have bronchiolitis by computed tomography. Patients who had ICD-10 diagnosis code J21 (acute bronchiolitis), ICD-10 diagnosis code E84 (cystic fibrosis), or who were <20 years old were excluded. Healthcare costs and the cause of in-hospital mortality were determined by the main ICD-10 code at the time of admission. Concomitant diseases were calculated as ICD-10

codes. ICD-code was J30 for rhinitis; J46 for asthma; I10–I13 for hypertension (HTN); K21 for gastroesophageal reflux disease (GERD); J01 or J32 for sinusitis; E10–E14 for diabetes mellitus; M80 or M81 for osteoporosis; G45, G46, I60–I63 for cerebrovascular disease (CVD); I20 for angina; I70 or I71 for peripheral vascular disease; I43 or I50 for congestive heart failure (CHF); F32 to F34 for depression; M05, M06, M32–M34 for rheumatologic disease; C1–C9 for cancer; K73 for liver disease; I21 or I22 for myocardial infarction; K50 or K51 for inflammatory bowel disease; and A31 for non-tuberculosis mycobacterium (NTM). Concomitant diseases were stratified into airway-specific conditions (rhinitis, sinusitis, asthma; airway inflammation diseases) and systemic conditions (HTN, GERD, osteoporosis, CVD, angina, peripheral vascular disease, CHF, depression, rheumatoid disease, cancer, liver disease, myocardial infarction, inflammatory bowel disease, NTM).

2.4. Control group (non-bronchiolitis group)

The control group was obtained by 1:1 propensity score (PS) matching considering age and sex. PS matching was performed using a “greedy nearest neighbor” algorithm with a 1:1 ratio. Confirmation whether PS matching was successful or not was judged by the absence or presence of major imbalances in the values or standardized mean differences (SMDs) in each group.

2.5. Statistical analysis

Data analysis was conducted between January 2002 and December 2013. All statistical analyses were performed using R version 3.53 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 14 (Stata Corp LLC, College Station, TX). “MatchIT,” “Dygraphs,” and “ggplot” packages were used for visualization in R package. The hazard ratio (HR) in the Cox Proportional-Hazards model was calculated considering the time variable (between the end point and start point of the study).

3. Results

3.1. Prevalence, comorbidity, healthcare costs, and mortality of the bronchiolitis group

In the first stage of the study, 1,125,691 individuals were randomly sampled from the 2002 to 2013 KNHIS-NSC database according to age, sex, residential area, and level of household income. In this period, a total of 817,427 patients were diagnosed with bronchiolitis. Among them, 308,264 patients were aged under 20 years and 175,766 patients were diagnosed with acute bronchiolitis. Finally, a total of 8258 patients having bronchiolitis from causes other than acute bronchiolitis was included in this study. The overall prevalence of bronchiolitis was 688 cases/1,000,000 population during the study period (95% confidence interval, 625–751) and the estimated prevalence of the disease was highest in 2002 (867 cases) and lowest in 2005 (467 cases) (Fig. 1). Among this group of patients, 4510 were men (54.6%) and the average age of patients was 62.6 ± 2.8 years. Bronchiolitis prevalence showed a peak incidence in patients in their 60s (Fig. 1).

The most common comorbid clinical condition in adults with bronchiolitis was rhinitis (52.3%), followed by bronchial asthma (52.23%), HTN (43.69%), GERD (30.56%), sinusitis

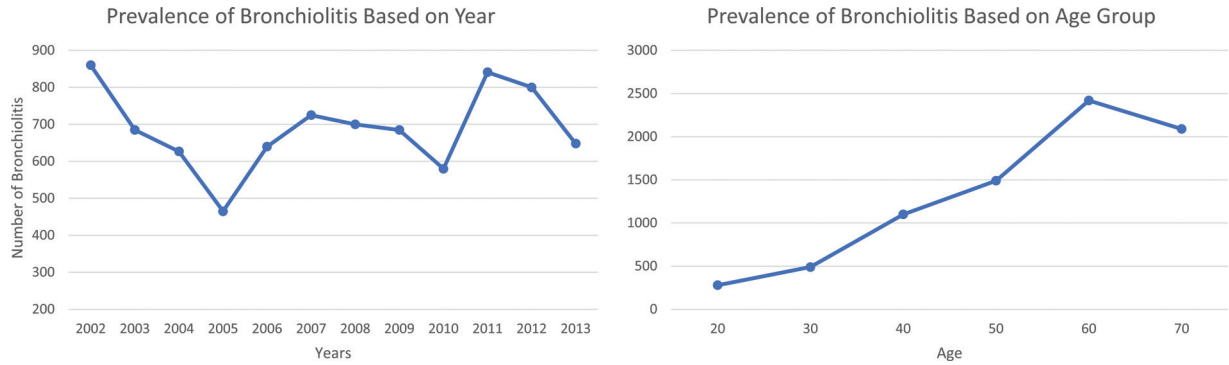


Figure 1. Prevalence of bronchiolitis, 2002 to 2013 and prevalence of bronchiolitis based on age group.

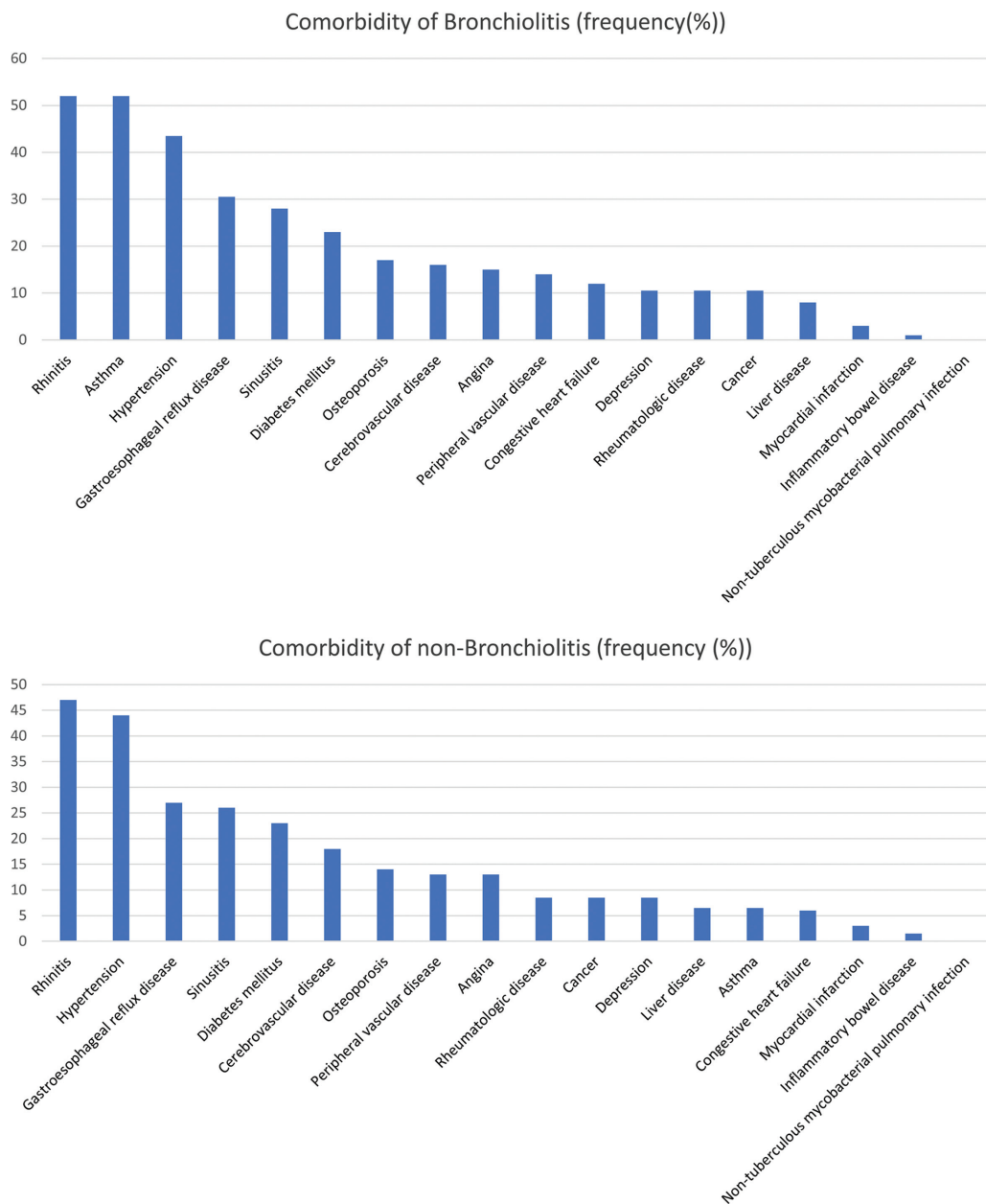


Figure 2. Concomitant diseases in the bronchiolitis and non-bronchiolitis groups (frequency [%]).

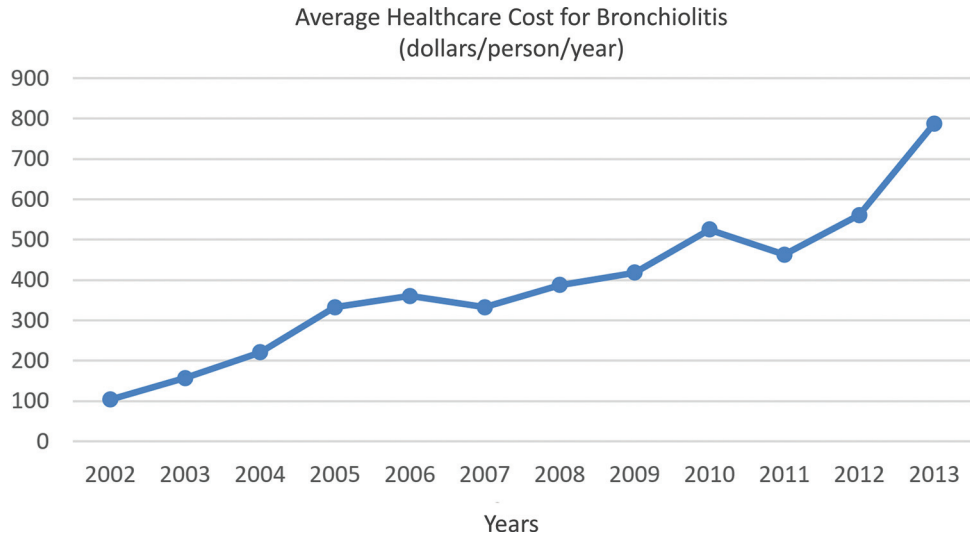


Figure 3. Healthcare expenditure regarding bronchiolitis (dollars per person per year).

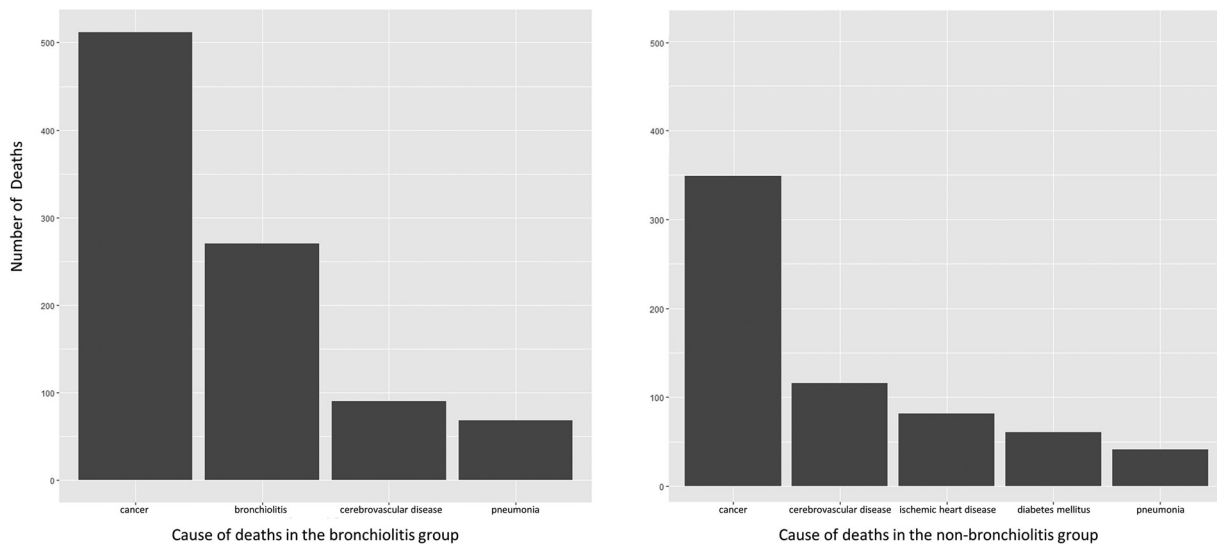


Figure 4. Mortality of the bronchiolitis and non-bronchiolitis groups (PS-matched). PS=propensity score.

(28.72%), diabetes mellitus (22.77%), and osteoporosis (17.85%). Other common bronchiolitis-associated comorbidities were CVD (16.86%), angina (14.37%), peripheral vascular disease (13.42%), CHF (11.9%), and malignancy in any organ (10.6%) (Fig. 2).

The average healthcare cost for adult bronchiolitis, combining diagnostic and therapeutic costs, was about 465,000 won (\$400 or EUR320)/person/yr with a dramatically increasing tendency over time (the lowest in 2002 at approximately 125,000 won [\$107 or EUR95]; the highest in 2013 at about 945,000 won [\$800 or EUR716]) (Fig. 3).

During the study period, the overall mortality in the adult bronchiolitis group was approximately 21.5% (1775 cases). Malignancy in any organ (6.2%, 512 cases) was the leading cause of mortality, followed by bronchiolitis itself (3.3%, 270 cases), cerebrovascular disease (0.8%, 68 cases), and pneumonia (0.8%, 68 cases) (Fig. 4). Among the malignant diseases, lung

cancer (46.7%, 229 cases) was the most common type of cancer accounting for nearly half of all cases, followed by a gastrointestinal origin of cancer (38.2%).

3.2. Comorbidity and mortality of the matched control group (non-bronchiolitis group)

The matched control group was well distributed regarding sex and age (Fig. 5, Table 1). All SMDs were <0.1 , which indicates that they were well distributed (Table 1). The comorbidities in the non-bronchiolitis group are shown in Fig. 2. The proportion of airway-specific conditions in the non-bronchiolitis group was significantly lower than in the bronchiolitis group, whereas systemic disease remained virtually unchanged (chi-squared test, $P < .05$).

The overall mortality in the matched non-bronchiolitis group was approximately 13.7% (1148 cases), which is significantly



Figure 5. Propensity score matching results regarding age and sex in the bronchiolitis and non-bronchiolitis groups.

Table 1

Demography of bronchiolitis and non-bronchiolitis groups.

Variable	Bronchiolitis group	Non-bronchiolitis group	SMD
Sex			0.00
Female	3803	3803	
Male	4572	4572	
Age			0.00
≥60	6179	6179	
40–59	1479	1479	
≤39	717	717	
SES			0.07
High	4384	4671	
Low	3991	3704	
RA			0.24
Seoul	1164	1954	
Rural	5230	4716	
Metro	1981	1705	
HTN			0.02
Yes	5361	5446	
No	3014	2929	
DM			0.02
Yes	3105	3042	
No	5270	5333	
Asthma			0.54
Yes	1492	184	
No	6883	8191	
Rhinitis			0.19
No	1794	2490	
Yes	6581	5885	

Table 1
(continued).

Variable	Bronchiolitis group	Non-bronchiolitis group	SMD
GERD			0.14
No	3687	4252	
Yes	4688	4123	
Sinusitis			0.11
No	4445	4901	
Yes	3930	3474	
Osteoporosis			0.13
No	5718	6204	
Yes	2657	2171	
CVD			0.04
Yes	5015	5185	
No	3360	3190	
Angina			0.09
No	6378	6689	
Yes	1997	1686	
PVD			0.02
No	7696	7746	
Yes	679	629	
CHF			0.23
No	7133	7745	
Yes	1242	630	
Depression			0.12
No	6613	7017	
Yes	1762	1358	
RD			0.08
No	6988	7241	
Yes	1387	1134	
Cancer			0.11
No	6584	6959	
Yes	1791	1416	
LD			0.08
No	7445	7634	
Yes	930	741	
MI			0.02
No	8008	8036	
Yes	367	339	
IBD			0.03
No	8217	8247	
Yes	158	128	
NTM			0.07
No	8327	8361	
Yes	48	14	

CHF = congestive heart failure, CVD = cerebrovascular disease, DM = diabetes mellitus, GERD = gastroesophageal reflux disease, HTN = hypertension, IBD = inflammatory bowel disease, LD = liver disease, MI = myocardial infarction, NTM infection = non-tuberculous mycobacterial pulmonary infection, PVD = peripheral vascular disease, RD = rheumatologic disease.

lower than in the bronchiolitis group ($P < .05$). Apart from bronchiolitis, the other causes of death in the bronchiolitis and non-bronchiolitis groups were similar (Fig. 4). Among the malignant diseases, a gastrointestinal origin of cancer (51.1%, 181 cases) accounted for half of all cases, followed by a respiratory origin of cancer (26.2%, 93 cases).

4. Discussion

This study reports the prevalence, comorbidities, mortality, and medical burden of adult bronchiolitis other than from infectious causes among an Asian population using nationwide health insurance data. The estimated prevalence of bronchiolitis was 688 cases per 1,000,000 of the population, so is not an uncommon disease in South Korea (Fig. 1). Although the prevalence of bronchiolitis was relatively constant throughout

the study period, the peak incidence of the disease in patients in their 60s is an impressive result (Fig. 1). So far, in the main age group, there have been no reports of bronchiolitis apart from in children.

Bronchiolitis is inflammation of airways <2 mm in diameter with absence of cartilage rings, alveolar ducts, and alveoli. Its location is strictly between 8th generation bronchi and terminal respiratory bronchiole. The relatively high prevalence of rhinitis and sinusitis among bronchiolitis patients is also quite interesting (Fig. 2). This may support the similarity or shared pathogenic mechanism existing between upper and lower respiratory tract disorders in the context of united airway disease.^[6,7] Approximately 80% of patients with asthma have rhinitis, and about 10% to 40% of patients with rhinitis have asthma.^[8] The upper and lower airways are called united airways because they are histologically similar to epithelial cells, goblet cells, basement

membrane, and lamina propria.^[9] The upper airway and the lower airway are similar in that they share effector cells such as mast cells, basophils, and eosinophils, and related cytokines and chemokines.^[10] Due to these structural and functional similarities, it is assumed that bronchiolitis is also associated with upper airway disease. There are reports that bronchiolitis is another pulmonary manifestation of GERD.^[11] The association with these various comorbidities means that bronchiolitis is considered to be an important disease that deserves re-examination. To understand these observations more clearly, we selected the age- and sex-matched non-bronchiolitis group and compared the underlying disease and mortality rates. In the non-bronchiolitis group, airway-specific conditions (rhinitis, sinusitis, and asthma) were significantly lower than in the bronchiolitis group ($P < .05$).

Healthcare costs for bronchiolitis showed a steep increase during the same period (Fig. 3). However, as mentioned earlier, increasing medical expenditure on bronchiolitis over time seems not to be associated with changes in prevalence of the disease, rather it may reflect an improvement in accessibility to healthcare services during this period.

The most common causes of death in the bronchiolitis group were any type of cancer, followed by bronchiolitis itself (Fig. 4). In the non-bronchiolitis group, other causes of death (cancer > CVD > pneumonia) were similar to those in the bronchiolitis group, except that mortality from bronchiolitis was significantly reduced. Bronchial or lung cancer (46.7% of total cancer) accounted for the majority of deaths in the bronchiolitis group. It is noteworthy that bronchiolitis results in a large proportion of deaths in the bronchiolitis group. Conversely, in the non-bronchiolitis group, a gastrointestinal origin of cancer (51.1% of all deaths from cancer) was the leading cause of death. A more careful diagnosis and treatment of adult bronchiolitis is required.

There are several points that should be considered in this study. First, the prevalence of bronchiolitis was estimated using the ICD-10 diagnosis code, which is based on health insurance claim data, thus potential errors could have been made here. Furthermore, the ICD-10 diagnosis code system itself is not sufficiently adequate for the optimal classification of adult bronchiolitis according to the diverse etiologies other than an infectious cause. Many bronchiolitis patients may be misclassified into subtypes of chronic obstructive pulmonary disease or bronchiolitis associated with acute airway infection (J21). Second, the KNHIS-NSC database for bronchiolitis is subject to potential errors if physicians fail to list the ICD-10 diagnosis code. Limited recognition of isolated forms of bronchiolitis^[1] or in association with major airway or alveolar diseases^[12,13] may compel clinicians to underestimate the clinical significance of the disease. Third, more specific information such as general medical history, laboratory data, and radiological findings for the patients were not available in the KNHIS database. Thus, more detailed analysis could not be performed.

To our knowledge, this is the first study on bronchiolitis to report its prevalence, comorbidities, medical expenditure, and causes of death. The estimated prevalence of bronchiolitis was 688

cases per 1,000,000 of the population. Common comorbidities were rhinitis, bronchial asthma, hypertension, gastroesophageal reflux disease, and rhinosinusitis. Malignancy in any organ was the leading cause of mortality in the patient group, followed by bronchiolitis itself. Further larger prospective multiethnic cohort studies should be carried out in the near future.

Author contributions

Jae Seok Jeong, conceptualization, data curation, and drafted the manuscript. **Jong Seung Kim**, conceptualization, formal analysis, supervision, and drafted the manuscript. **Sang Woo Yeom**, **Min Gyu Lee**, and **Yeon Seok You** data curation, formal analysis. **Yong Chul Lee**, conceptualization, data curation, and drafted and edited the manuscript.

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